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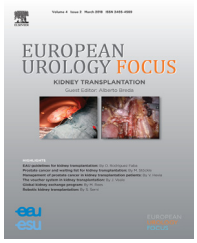

Prostate Cancer

Evolution of Targeted Prostate Biopsy by Adding Micro-Ultrasound to the Magnetic Resonance Imaging Pathway

Laura Wiemer[a,†], *Markus Hollenbach*[a,†], *Robin Heckmann*[a], *Beatrice Kittner*[a], *Henning Plage*[a], *Max Reimann*[a], *Patrick Asbach*[b], *Frank Friedersdorff*[a], *Thorsten Schlomm*[a], *Sebastian Hofbauer*[a,‡], *Hannes Cash*[a,‡,*]

[a] *Department of Urology, Charité—University Medicine Berlin, Berlin, Germany;* [b] *Department of Radiology, Charité—University Medicine Berlin, Berlin, Germany*

Article info

Article history:
Accepted June 27, 2020

Associate Editor:
Christian Gratzke

Keywords:
Prostate biopsy
Microultrasound
Target biopsy
Multiparametric magnetic resonance imaging
Prostate cancer

Abstract

Background: Although multiparametric magnetic resonance imaging (mpMRI) revolutionized the implementation of prostate biopsies, a considerable amount of clinically significant prostate cancer (csPCa) is missed when performing mpMRI-targeted biopsies only. Micro-ultrasound (micro-US) is a new modality that allows real-time targeting of suspicious regions.
Objective: To evaluate micro-US of the prostate with real-time targeting of suspicious regions in patients suspected to have prostate cancer (PCa).
Design, setting, and participants: We examined 159 patients with prior mpMRI and suspicion of PCa with micro-US in the period from February to December 2018. Micro-US lesions were documented according to the prostate risk identification for micro-US (PRI-MUS) protocol, and were blinded to the mpMRI results and targeted independently of the mpMRI lesions.
Outcome measurements and statistical analysis: The main outcomes were cancer detection rate, additional detection of csPCa, and International Society of Urological Pathology (ISUP) grade group upgrading via micro-US.
Results and limitations: PCa was found in 113/159 (71%) men, with 49% (78/159) having clinically significant cancer (csPCa; ISUP $\geq$ 2). Micro-US–targeted biopsies resulted in a higher ISUP grade group than the nontargeted biopsies in 26% (42/159), compared with both nontargeted and MRI-targeted biopsies in 16% (26/159). In 17% (27/159) of patients, targeted mpMRI–guided biopsy was negative with cancer identified in the micro-US–guided biopsy, of whom 20 had csPCa. The comparison with only MRI-positive patients is the main limitation of this analysis.
Conclusions: Our data show an added benefit of micro-US in addition to mpMRI-targeted biopsies in a population of men at risk of PCa. A novel biopsy protocol with solely targeted biopsy with micro-US and mpMRI seems possible, replacing conventional ultrasound and omitting standard systematic biopsies.
Patient summary: In this report, we looked at the performance of microultrasound in the setting of diagnosing prostate cancer. We found that microultrasound is a good addition to magnetic resonance imaging (MRI) of the prostate and presents an alternative for men who may not undergo MRI.

† These authors contribute equally.
‡ These authors contribute equally.
* Corresponding author. Department of Urology, Charité—Universitätsmedizin Berlin, Hindenburgdamm 30, Berlin 12203, Germany. Tel. +4930450515172.
E-mail address: hannes.cash@charite.de (H. Cash).

https://doi.org/10.1016/j.euf.2020.06.022
2405-4569/

1. Introduction

Multiparametric magnetic resonance imaging (mpMRI) has become the new diagnostic standard for men at risk of clinically significant prostate cancer (csPCa) [1–4]. The updated clinical guidelines now recommend performing prostate mpMRI either prior to the first biopsy or after initial negative standard transrectal ultrasound (TRUS)-guided prostate biopsy [5,6]. The PRECISION trial showed that magnetic resonance imaging (MRI)-targeted biopsies alone were superior to standard TRUS-guided biopsy in detecting csPCa in the primary biopsy setting while reducing the rate of insignificant prostate cancer (PCa) [1]. However, other studies showed that systematic TRUS biopsies lead to an increase in the detection of csPCa by 4–16% and in the overall detection of PCa by around 30% [2,4,7,8]. Regardless of the approach used to sample MRI targets (software-assisted fusion, robotic fusion, or cognitive fusion biopsy), reports have demonstrated consistency in detecting both csPCa and less clinically insignificant cancer [2].

It has been suggested that an increase in the number of mpMRI scans may lead to issues with widespread availability, waiting times, and increased costs [9]. Further challenges include the training of dedicated uroradiologists and the variability in Prostate Imaging Reporting and Data System (PI-RADS) reporting between radiologists [10]. In addition, the mpMRI pathway faces challenges with varied standards in image quality, attributable to magnet strength, patient movement, or inability of men to undergo mpMRI for a variety of reasons [11].

There is a new debate on the various suggested MRI-directed biopsy pathways, each of which has potential limitations and benefits [7]. Some authors also promote target saturation of the mpMRI lesion, which was also introduced by the PI-RADS steering committee with the term sampling of the "penumbra" [12]. Various authors have shown that more csPCa cases are detected with a large number of core biopsy samples per index lesion, especially in PI-RADS 4 and 5 lesions [13,14]. Novel technologies such as microultrasound (micro-US) may further improve MRI-directed biopsy or add an independent value to the PCa pathway [15].

The use of a novel micro-US system with improved resolution to 70 μm and operating at frequencies up to 29 MHz allows for a detailed ultrasound examination of the prostate, giving the operator the ability to visualize potential targets in real time while also adding MRI/ultrasound fusion [16]. We analyzed the diagnostic value of adding micro-US in a consecutive cohort of men undergoing an MRI/ultrasound-fusion–guided prostate biopsy.

2. Patients and methods

2.1. Patients

In the period from February 2018 to December 2018, men at a clinical risk of PCa underwent high-resolution transrectal prostate biopsy using the

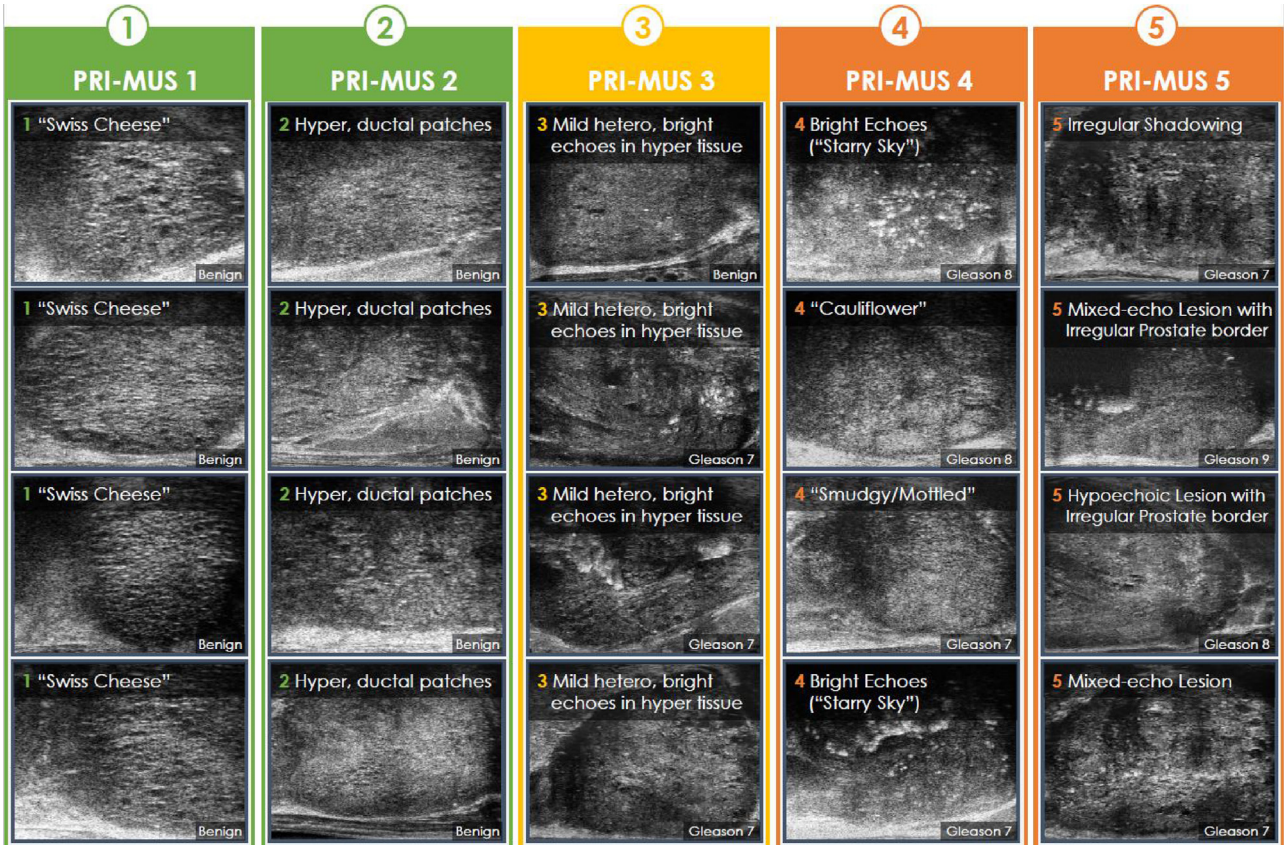

Fig. 1 – Examples of PRI-MUS grades. PRI-MUS = prostate risk identification for microultrasound.

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ExactVu micro-US system. All men had a mpMRI scan prior to prostate biopsy. The study was approved by the local ethics committee (IRB number: EA4/067/18).

2.2. MRI and MRI-targeted biopsy

Multiparametric MRI was performed at our institution with a 3.0-T scanner with a pelvic phased-array coil without an endorectal coil. The imaging protocol included high-spatial-resolution T2-weighted turbo spin-echo sequences in transverse and coronal orientation and transverse diffusion-weighted images (measured *b* values 0, 500, and 1000s/mm^2, calculated *b* value 1400s/mm^2), and when indicated based on the PI-RADS category of the dominant sequence, a dynamic contrast-enhanced sequence. All patients who underwent mpMRI were analyzed with PI-RADS version 2 [17].

The MRI-targeted biopsies were performed with the FusionVu feature on the ExactVu system. An independent examiner marked the MRI targets. The doctor performing the biopsies was blinded to mpMRI results when performing the micro-US assessment. Targets were defined as a score of ≥3 in prostate risk identification for micro-US (PRI-MUS) or PI-RADS systems.

2.3. Microultrasound

Real-time evaluation of the prostate was performed using the PRI-MUS protocol [18] for assigning a risk assessment to prostate tissue (Fig. 1) by an operator blinded to the results of the associated mpMRI and to the patient's medical history. All patients underwent micro-US–guided targeted biopsy of any identified suspicious PRI-MUS regions as part of a 10-core "systematic" biopsy, with a minimum of two cores taken per target, ± a fusion biopsy of the MRI lesion (Fig. 2). The mpMRI lesion was unblinded before performing the targeted biopsies. As a result of this procedure, our "systematic" biopsy samples will be termed "nontargeted" in this analysis.

2.4. Biopsy procedure

Biopsies were performed transrectally by one of the three urologists experienced in performing MRI-targeted biopsies and standard transrectal ultrasound. All operators received a standardized training program from Exact Imaging prior to performing micro-US of the prostate and applying the PRI-MUS rating. The training period covered 15 expert-proctored cases. All operators were assessed over their first 10 cases after

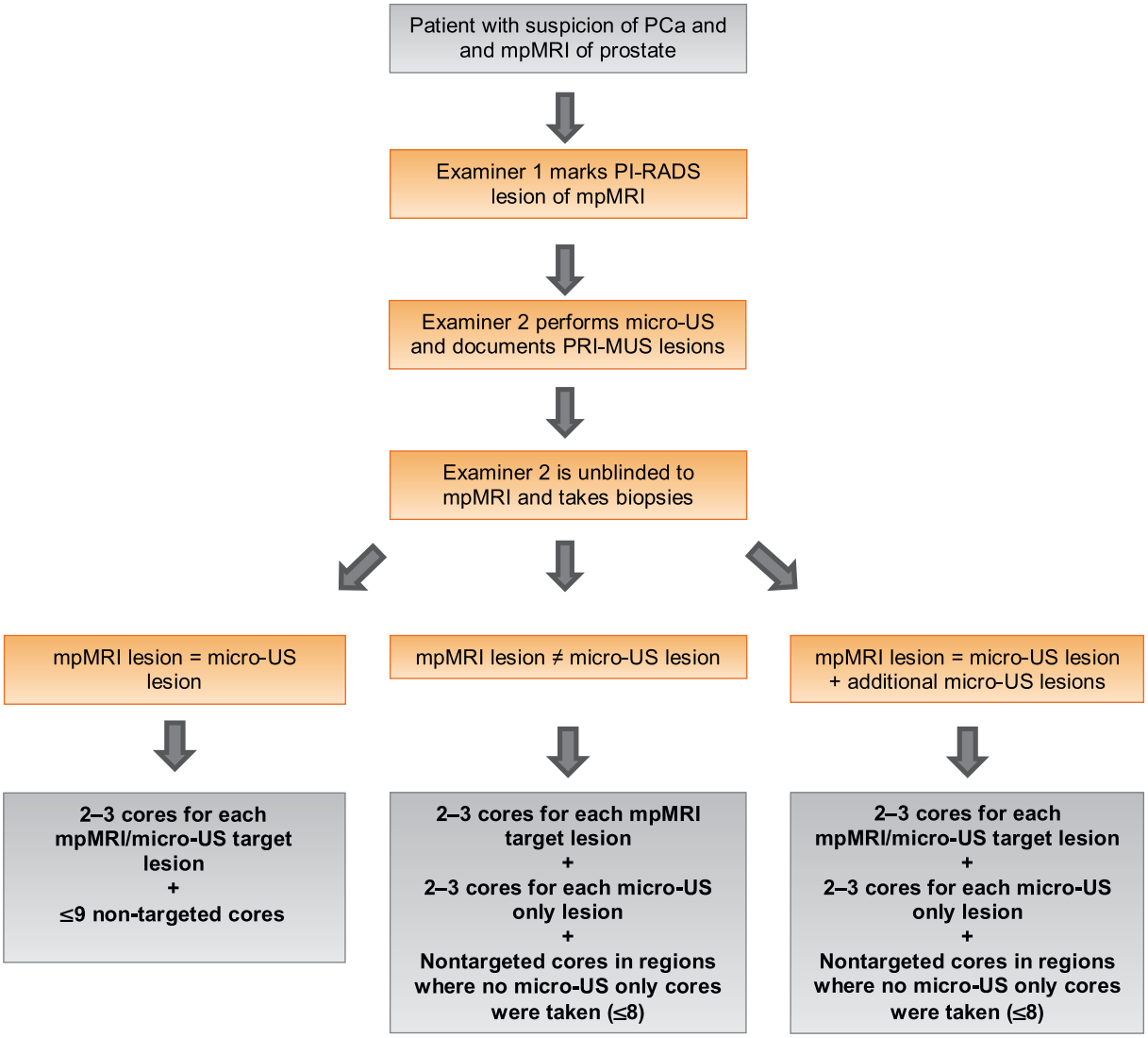

Fig. 2 – Biopsy workflow. micro-US = microultrasound; mpMRI = multiparametric magnetic resonance imaging; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PRI-MUS = prostate risk identification for microultrasound.

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training and found to be able to detect PRI-MUS lesions correctly. The micro-US targets were documented on a standardized worksheet (Supplementary Fig. 1). A target was defined as a PRI-MUS score of ≥3. Regions without micro-US targets were sampled systematically. All patients received a nontargeted biopsy in addition to targeted cores. After assigning PRI-MUS lesions independently of the mpMRI, the examiners were unblinded and the micro-US– and MRI-targeted biopsies were taken (minimum two cores per target). If MRI and micro-US targets were identical, this was documented, and no additional samples were taken (Fig. 2). Biopsy cores were submitted individually by prostate region. The cores were analyzed by specialized uropathologists using the International Society of Urological Pathology (ISUP) Gleason system [19].

2.5. Statistical analysis

Clinically significant PCa was defined as those with an ISUP grade group (GG) of ≥2. Confidence intervals (CIs) and comparison p values were calculated using the Jefferys interval in MATLAB. Numbers are given as median + interquartile range (IQR).

3. Results

Study demographics are summarized in Table 1. The median prostate-specific antigen level of patients was 7.59 ng/mL (IQR 5.78–11.5). Of the patients, 79 (45%) received primary biopsy, while 88 (55%) had had previous prostate biopsies before. Of 159 patients, 42 (26%) had a positive digital rectal examination. The median prostate volume was 53 cc, and no selection was performed to limit application of micro-US based on prostate size. The median number of cores was 14 (12–15). PCa was found in 113/159 (71%) men, with 78 (49%) having csPCa.

Relative sensitivity of micro-USA for csPCa detection was 95% (95% CI 88–98%), with 74/78 csPCa cases identified correctly; micro-US specificity in predicting csPCa was 15% (12 of 81 cases [95% CI 8–24%]).

Table 1 – Study demographics.

Characteristic	Value
Age (yr), median (IQR)	70 (64–74)
PSA (ng/mL), median (IQR)	7.59 (5.78–11.5)
Volume (cc), median (IQR)	53 (35.5–76.5)
Men under active surveillance, *n* (%)	46 (29)
Prior negative biopsies, *n* (%)	42 (26)
Abnormal digital rectal examination, *n* (%)	42 (26)
PI-RADS distribution among patients with mpMRI, *n* (%)	
1	3 (2)
2	4 (3)
3	15 (9)
4	74 (47)
5	63 (40)
PRI-MUS distribution among patients with, *n* (%)	
1	13 (8)
2	3 (2)
3	22 (14)
4	74 (47)
5	47 (30)
Cores taken overall, median (IQR)	14 (12–15)
Cores micro-US targets, median (IQR)	6 (2–9)
Cores mpMRI targets, median (IQR)	2 (2–2)
Cores nontargeted, median (IQR)	6 (5–8)

IQR = interquartile range; micro-US = microultrasound; mpMRI = multiparametric magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and Data System; PRI-MUS = prostate risk identification for micro-US; PSA = prostate-specific antigen.

For micro-US, the patient-level negative predictive value for any PCa was 75% (95% CI 51–91%), while the positive predictive value was 52% (95% CI 44–60%).

The lesion-level positive predictive value for csPCa was 41% (95% CI 34–49%) for micro-US and 30% (95% CI 23–37%) for mpMRI (micro-US higher with p = 0.02).

In 92/159 patients (58%), the maximal ISUP GG values in the samples of the mpMRI and micro-US targets were identical, independent of the target location or lesion concordance. Of those, 54 (34%) were benign, 16 (10%) ISUP GG 1, and 22 (14%) ISUP GG ≥ 2 (Table 2). MRI targets upgraded the ISUP GG, compared with nontargeted biopsy in 34 patients (21%) and micro-US targets and nontargeted biopsies in 11 patients (7%). Micro-US–targeted biopsy showed a higher ISUP GG than the nontargeted biopsies in 26% (42/159) and both nontargeted and MRI-targeted biopsies in 16% (26/159). In total, micro-US targeting led to an ISUP GG upgrade in 9.4% more patients than mpMRI targeting (95% CI 2.2–16.5%, p = 0.005).

In 17/159 patients (11%), micro-US–targeted biopsy detected high-risk carcinomas (ISUP ≥ 4, Gleason score ≥8), while mpMRI-guided fusion biopsy alone showed only ISUP < 4 cancer. Twelve (8%) of these men did not have any PCa on MRI targets. The added value in micro-US targets on top of nontargeted and mpMRI targeted samples was 17% (95% CI 11–23%) for csPCa and 8% (95% CI 5–13%) for high-risk carcinomas.

Twenty-five patients were found to have a higher ISUP GG through mpMRI-targeted biopsy (16%; Table 2 and Fig. 3). In 27 patients (17%), micro-US–guided biopsy identified cancer where the mpMRI-targeted-only biopsy was negative; of these patients, 20 had csPCa. In eight (5%) cases, nontargeted biopsy alone (MRI + micro-US target biopsy negative) revealed PCa, of which three cases were csPCa. A total of 1322 nontargeted regions were considered nonsuspicious on mpMRI and micro-US. This could have eliminated approximately eight cores per patient. Looking at the different biopsy strategies, we found 52 insignificant cancers in nontargeted biopsies, 33 in MRI-targeted biopsies, and 27 in micro-US targets (Fig. 4). Addition of micro-US to our biopsy strategy leads to an increased detection of csPCa without increasing the rate of insignificant PCa.

The detection rates in relation to the PRI-MUS score were 68% (32/47) for PRI-MUS 5, 47% (35/74) for PRI-MUS 4, and 31% (7/22) for PRI-MUS 3. Four csPCa were diagnosed in PRI-MUS 1/2 lesions. The detection rates were 93% (55/59) for PI-RADS 5 lesions, 68% (50/73) for PI-RADS 4 lesions, and 23% (5/22) for PI-RADS 3 lesions.

4. Discussion

We evaluated the initial performance of micro-US and the PRI-MUS scoring system in a prospective cohort of men at risk for PCa. This preliminary experience showed an added value in detecting csPCa in addition to mpMRI-targeted biopsy. If only targeted biopsies of PRI-MUS and PI-RADS lesions had been performed, only five (3%) csPCa cases

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Table 2 – Distribution of ISUP grade groups among targeted biopsies.

		mpMRI target					
micro-US target	ISUP	**0**	**1**	**2**	**3**	**4**	**5**
	0	54	10	6	2	0	1
	1	7	16	3	0	1	0
	2	6	5	8	2	0	0
	3	2	2	2	2	0	0
	4	6	0	2	1	8	0
	5	6	0	1	1	1	4

ISUP= International Society of Urological Pathology, mpMRI= multiparametric Magnetic Resonance Imaging, micro-US= micro-ultrasound.
Example: There was one ISUP grade 5 prostate cancer diagnosed due to mpMRI target which was not suspicious in micro-US (first column) while there 6 ISUP grade 5 prostate cancers diagnosed due to micro-US which did not seem get a PI-RADS rating on mpMRI (first row).

would have been missed, and 1322 cores or eight cores per patient could have been omitted. In total, 17 patients (11%) with high-risk carcinomas (ISUP ≥ 4) were identified, which would have been missed by a mpMRI-targeted-only biopsy.

The mpMRI pathway followed by MRI-targeted biopsies has shown an improvement in the detection of csPCa and has the potential to avoid unnecessary biopsies in 27–28% men with negative MRI [1]. However, there remain some limitations, mainly due to potential cost and availability. Concerning cost effectiveness, Faria et al [20] and Barnett et al [21] were able to show that an MRI first strategy is able to reduce the number of screening biopsies and therefore the long-term costs of overdiagnosis.

Multiparametric MRI is not yet the perfect tool, as approximately 16–35% of MRI lesions that harbor csPCa are either invisible or greatly underestimated by mpMRI [22,23]. Although, PI-RADS version 2 has improved intraobserver reproducibility, both performing mpMRI and interpreting PI-RADS results still introduce a potential source of error [24]. Furthermore, there is an ongoing discussion on the value of an added systematic biopsy, increasing the rate of csPCa in up to 16% compared with a targeted-only approach [8]. On the contrary, addition of systematic biopsies leads to an increase in total samples and the rate of insignificant cancers [2,7].

Schoots et al [7] discussed different biopsy strategies based on the available data of the Cochrane diagnostic test accuracy systematic review. While MRI- and triage-focused pathways maximize the detection of significant disease in MRI-positive men at a cost of nondetection of significant disease in MRI-negative men, detection-focused pathways will lead to an increase of biopsy cores and overdiagnoses of ISUP grade 1 cancers, but with the advantage of increasing the detection of significant disease (28%) [7].

Similar to micro-US, other approaches such as contrast enhanced ultrasound (CEUS) or multiparametric ultrasound using B mode, shear wave elastography, and CEUS with quantification software are trying to improve prostate ultrasound. Sensitivity of multiparametric ultrasound for csPCa is as high as 74% [25]. Attempts to analyze quantitative parameters in CEUS have been made, and might be able to determine cancer location and aggressiveness, and even machine learning and identification of risk areas might be feasible technically [26,27]. Owing to its complexity, it currently presents a tool used in expert centers and larger randomized studies are pending.

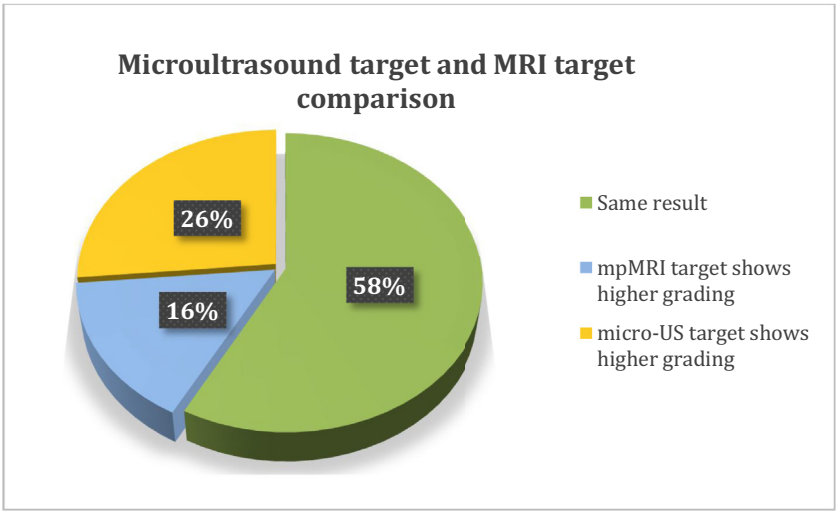

Fig. 3 – Distribution of ISUP grade groups among targeted biopsies. ISUP = International Society of Urological Pathology; micro-US = microultrasound; mpMRI = multiparametric magnetic resonance imaging; MRI = multiparametric magnetic resonance imaging.

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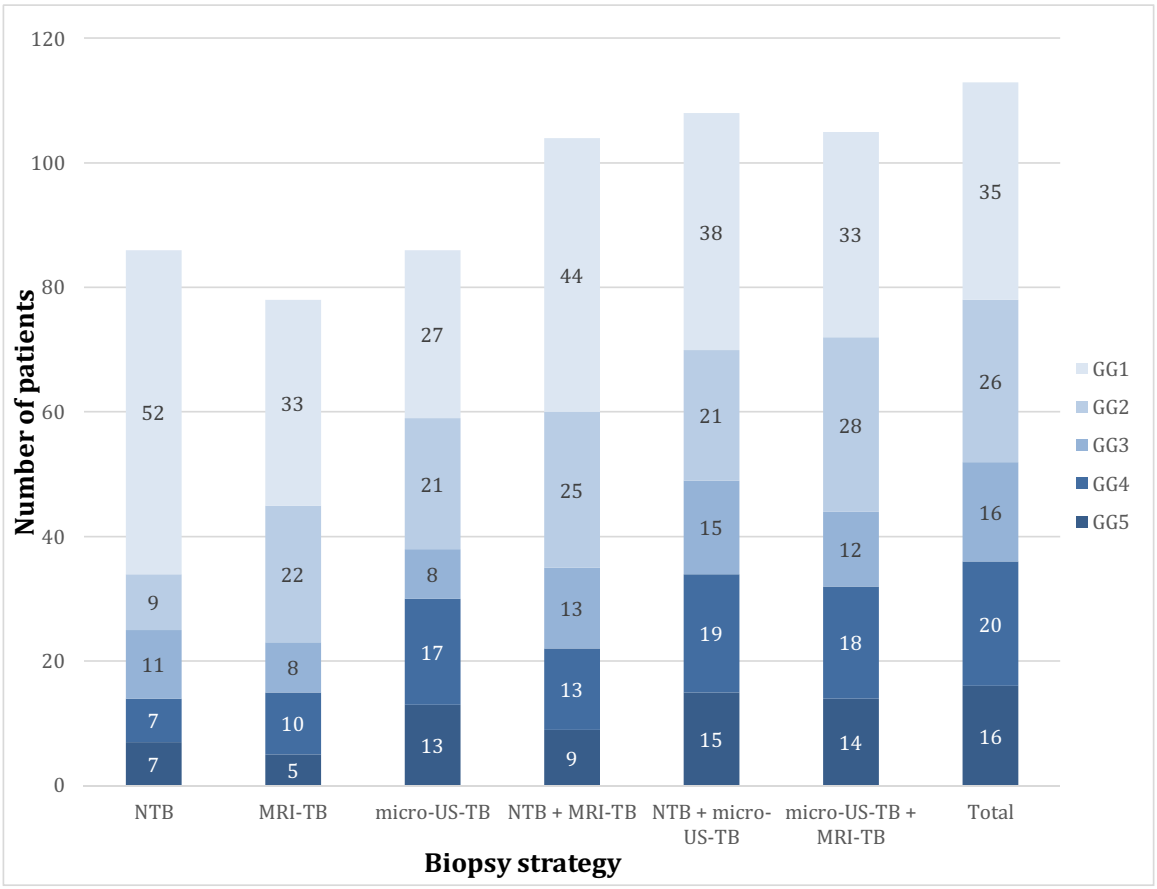

NTB= non targeted biopsy, MRI-TB= Magnetic Resonance Imaging-targeted biopsy micro-US-TB= micro-ultrasound targeted biopsy, GG= ISUP grade group

Fig. 4 – Distribution of grade groups depending on different biopsy strategies. GG = ISUP grade group; ISUP = International Society of Urological Pathology; micro-US-TB = microultrasound-targeted biopsy; MRI-TB = magnetic resonance imaging–targeted biopsy; NTB = nontargeted biopsy.

Several other studies using micro-US have shown its benefit in diagnosing csPCa [16,28–30]. A review of the results and their clinical implications has been published recently [15]. Lughezzani et al [16] were able to show micro-US sensitivity of 94% and a detection rate of 54% for csPCa. Comparing micro-US with mpMRI, they found 45% concordant lesions (39% csPCa) and another 16% csPCa in nonconcordant lesions. In our cohort, we detected 58% concordant lesions, of which 46% showed csPCa. The improvement may be due to our higher overall detection rate of 71%. In addition, Abouassaly et al [28] and Eure et al [31] were able to show additional detection of cancer and upgrading of ISUP GG comparing mpMRI and micro-US in small cohorts. Furthermore, there is evidence that MRI cognitive guided micro-US biopsies show a higher csPCa detection rate than perineal robotic ultrasound-MRI fusion biopsies [30].

Several limitations of our data should be noted. This is an analysis of our first patients examined with micro-US. Although all operators received standardized training from Exact Imaging, a learning curve effect might have biased our results. We analyzed all patients with the indication for a prostate biopsy who came to our institution in the given time frame, regardless of prostate size or biopsy indication. We also included patients under active surveillance, although the examiner did not know this information before documenting the PRI-MUS lesions. This may have led to a higher number of targets and may also have increased cancer detection. Furthermore, previous biopsies potentially produce artifacts. Information on such artifacts, which might have influenced the biopsy, were not collected. The element of operator bias cannot be excluded since our patients were men with positive mpMRI, and it can be argued that in such a cohort, both systematic and micro-US biopsies would be expected to perform well. Without an accurate reference standard (ie, saturation/template biopsy/whole gland pathology), it is not possible to determine absolute sensitivity; however, we calculated the relative sensitivity of micro-US compared with cancers detected by the full biopsy protocol. Sensitivity, specificity, and negative predictive values for mpMRI could not be determined as only mpMRI-positive individuals were included. When we found a micro-US target in a specific field, we did not take another nontargeted core from the same field in order to reduce the number of cores taken. Therefore, we cannot compare with standard systematic biopsy and instead refer only to nontargeted biopsies. MRI targets were taken by the FusionVu system included in ExactVu micro-US machine; we do not know whether this system differs in quality from

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our previous MRI-fusion systems. However, other investigators have demonstrated comparable results [30]. We have to note that our experience with the PRI-MUS rating system on micro-US changed during the course of the study due to a learning curve.

Our analysis shows the benefits of micro-US with the potential to further improve MRI/ultrasound-guided targeted biopsy. The real-time sampling of both micro-US and mpMRI lesions showed increased diagnostic accuracy, while reducing the numbers of biopsy samples. Therefore, the potential exists to perform only targeted biopsies (MRI and micro-US), saving unnecessary systematic biopsies. Prospective multicenter analyses are needed for the analysis of inter-reader variability of the PRI-MUS scoring protocol, and well-designed prospective trials are needed to evaluate the value of micro-US compared with mpMRI before the initial biopsy.

5. Conclusions

Our analysis showed an added benefit of micro-US when added to mpMRI-targeted biopsies in a population of men at risk of PCa. We propose a novel biopsy approach using only micro-US– and mpMRI-targeted biopsy without systematic biopsy, which warrants further investigation.

Author contributions: Hannes Cash had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Cash, Wiemer.
Acquisition of data: Wiemer, Hollenbach, Hobauer, Heckmann, Kittner, Plage, Reimann, Asbach.
Analysis and interpretation of data: Wiemer, Hobauer, Cash.
Drafting of the manuscript: Wiemer, Cash, Hobauer, Hollenbach.
Critical revision of the manuscript for important intellectual content: Hobauer, Friedersdorff, Asbach, Schlomm.
Statistical analysis: Wiemer, Hobauer, Hollenbach.
Obtaining funding: Cash.
Administrative, technical, or material support: None.
Supervision: Cash, Schlomm.
Other: None.

Financial disclosures: Hannes Cash certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: L. Wiemer and H. Cash received honoraria for contributing to a workshop for Exact Imaging Inc. All other authors have nothing to declare.

***Funding/Support and role of the sponsor*:** The study was supported by Exact Imaging Inc., Toronto, Canada, with material support, data management, and analysis. There was no additional funding.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.euf.2020.06.022.

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Please cite this article in press as: Wiemer L, et al. Evolution of Targeted Prostate Biopsy by Adding Micro-Ultrasound to the Magnetic Resonance Imaging Pathway. Eur Urol Focus (2020), https://doi.org/10.1016/j.euf.2020.06.022